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The relationship between vitamin D deficiency and the frequency of Helicobacter Pylori and peptic ulcer in childhood

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Abstract
Aim: In the present study, the purpose was to examine the relation between Vitamin D deficiency, and the presence of Helicobacter Pylori (HP) and peptic ulcer.
Material and Methods: A total of 291 patients who presented to our Pediatric Gastroenterology Clinic with dyspeptic complaints were included in the study. The age, gender, and Vitamin D levels, endoscopic and histopathological findings of patients with and without Vitamin D deficiency were compared. Patients with peptic ulcers were compared in terms of Vitamin D levels and HP prevalence.
Results: Vitamin D deficiency was found to be higher in men. Although 70% of patients who had Vitamin D deficiency tested positive for HP, it was detected in 33% of patients without Vitamin D deficiency. In 19% of patients who had Vitamin D deficiency, there were peptic ulcers, and 9% of patients without Vitamin D deficiency had peptic ulcers, and the difference was statistically significant. Although the mean Vitamin D level in patients who had peptic ulcer was 15.8 ng/ml, it was 23 ng/ml in patients without peptic ulcers, and the difference was statistically significant (P=0.003). A total of 61% of patients with peptic ulcer had Vitamin D deficiency, 39% of patients without peptic ulcer had Vitamin D deficiency, and the difference was statistically significant.
Discussion: No effect of Vitamin D level on HP prevalence was detected. Since Vitamin D levels may be lower in patients who have peptic ulcer, Vitamin D levels must be examined in such patients.

Keywords
Endoscopy; Helicobacter Pylori; Vitamin D

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Introduction

Helicobacter Pylori (HP) is a gram-negative bacterium in spiral form colonizing in the gastric mucosa, and is the most common cause of resistant bacterial infection in the world [1]. HP localizes in the gastric mucosa, causing diseases such as peptic ulcer, B-Cell Lymphoma and gastric cancer as well as gastritis [2].

Vitamin D is a fat-soluble vitamin, and robust small intestines, sufficient amount of bile, and pancreatic secretion are required for its absorption. For this reason, many diseases of the gastrointestinal tract in children affect Vitamin D levels [3]. Vitamin D is a powerful immunomodulator other than calcium hemostasis. Different forms of Vitamin D have immunomodulatory effects on T and B-lymphocytes. Vitamin D also inhibits cellular differentiation, proliferation, and apoptosis [4], and is important in controlling the inflammation in HP infection. Some conflicting results have been reported that vitamin D deficiency may negatively affect the immune system and cause allergic diseases. Recently, a study conducted by Dogan et al.claimed that vitamin D deficiency may not play a role in the etiology and physiopathology of allergic gastrointestinal diseases like cow's milk protein allergy [5]. Previous studies have shown that active Vitamin D use reduces HP infection by more than 50% [6]. It has been reported with the recent discovery of Vitamin D receptors in different tissues that Vitamin D plays roles in diabetes, cardiovascular diseases, as well as in allergic, immunological and inflammatory diseases [7].

Peptic ulcer is generally seen in HP infection, nonsteroidal anti-inflammatory drugs, systemic diseases, and stress [8-10]. No studies investigating the relations between peptic ulcer and Vitamin D deficiency in the child age group were found in the literature. Many factors that affect immunity also have effects on HP infection. One of these factors is Vitamin D. The purpose of the present study was to determine the relations between Vitamin D deficiency and HP presence and peptic ulcer.

Material and Methods

A total of 291 patients who admitted to the University of Health Sciences, Van Education and Research Hospital, Children's Gastroenterology Clinic with recurrent abdominal pain and dyspeptic complaints, and who underwent gastric tissue biopsy with endoscopy of the upper gastrointestinal tract between April 2017 and April 2019 were included in the study.

The inclusion criteria for the study were age 1-18 years, the ability to undergo endoscopy of the upper gastrointestinal tract, no previous eradication therapy for HP, and volunteering to participate in the study.

Exclusion criteria for the study were as follows: 1) the use of drugs that might affect the metabolism of Calcium and Vitamin D (Calcium, Vitamin D, bisphosphonates, calcitonin, selective estrogen receptor modulators, anti-epileptic drugs, thyroid hormone drugs, steroids and colchicine); 2) the presence of liver and kidney disease, Cushing Syndrome, Diabetes Mellitus, thyroid diseases, bone diseases, rheumatological and autoimmune diseases that affect Vitamin D metabolism, 3) the use of proton pump inhibitors, H2 receptor blockers, bismuth compounds, and antibiotics in the last month; 4) previous gastric and intestinal surgeries; 5) being over the age of eighteen.

The demographic data (age, gender), and Vitamin D levels of all patients were documented, and 25(OH) Vitamin D levels in the blood were measured with Vitamin D Kit Electrochemiluminescence Method. Those whose laboratory data did not comply with the hospital standard values were not included in the study. Vitamin D values >20 ng/ml were evaluated as normal, and those under 20 ng/ml were evaluated as Vitamin D deficiency [11].

Endoscopy of the patients was performed in the Endoscopy Unit of Van Training and Research Hospital using a Fujinon EG530WR Endoscopy Device. All patients fasted for 6 hours before endoscopy. The patients were sedated with Midazolam 0.1 mg/kg and Ketamine 1 mg/kg after local pharyngeal xylocaine anesthesia, after which the endoscopic procedure was initiated. During endoscopy, the esophagus, cardia, fundus, corpus and antrum regions of the stomach were examined respectively in detail along with the duodenum. Endoscopic evaluations of the patients, the presence of esophagitis, the appearance of gastric mucosa, the appearance of bulbous and duodenum, the presence of peptic ulcer and endoscopic diagnosis were recorded.

The corpus, antrum, and duodenal biopsies that were taken endoscopically were sent to the pathology laboratory in 10% formaldehyde. After the routine tissue follow-up procedures, tissue samples were embedded in paraffin, cut into 5-micron sections, stained with routine Hematoxylin - Eosin (H-E), and were then evaluated under the light microscope. Then, the sections were stained with modified Giemsa to evaluate the presence of HP. Biopsies were reported according to the updated Sydney Classification (inflammation, activation, dysplasia, intestinal metaplasia, atrophy, and HP density).

The patients were divided into two groups as those with and without Vitamin D deficiency, and were compared in terms of age, gender, White Blood Cell (WBC), Hemoglobin (HBG), Platelet, Vitamin D levels, vitamin D deficiency, and the presence of HP. Also, Vitamin D levels, Vitamin D deficiency, and presence of HP were compared in patients with and without duodenal ulcer.

Ethics statement

All participants provided written permission to participate in the study. The ethical approval was obtained from the Ethics Committee of our hospital for this study (Approval number 19/01, Van/Turkey). All procedures were in line with the ethical standards of the human testing committee of our institution and the Helsinki Declaration. Written informed consent forms were obtained from all participants, who were evaluated by a gastroenterologist and then included in the study.

Statistical Analysis

The normality of the distribution of continuous variables was tested by the Shapiro- Wilk test. The Mann-Whitney U test was used to compare 2 independent groups for non-normal data and the Chi-square test was applied to investigate the relationship between 2 categorical variables. Multivariate logistic regression analysis was performed to adjust the effect of gender from results. ROC curve analysis was performed to determine the diagnostic value of Vitamin D levels. Statistical analysis was performed with SPSS for Windows version 24.0 and a P -value < 0.05 was accepted as statistically significant.

Results

Among the 291 patients who were included in the present study, 197 (68%) were boys and 94 (32%) were girls. The mean age of the patients was 12.7±3.9 years. HP was detected in 199 (68%) patients. Vitamin D deficiency was detected in 121 (42%) patients. The mean Vitamin D level was 20.7±9 ng/ml in all patients.

The mean age of patients with Vitamin D deficiency was 15 years, and the mean age of patients with normal Vitamin D levels was 14 years; and 31/121 (26%) of patients with vitamin D deficiency were girls, and 90/121 (74%) were boys; 63/170 (37%) of patients without vitamin D deficiency were girls, and 107/170 (63%) were boys. Vitamin D deficiency was significantly higher in boys (P=0.040). HP positivity was detected in 85/121 (70%) of patients with vitamin D deficiency, and in 56/170 (33%) of patients without vitamin D deficiency. A total of 23/121 (19%) of patients with vitamin D deficiency had peptic ulcer, 15/170 (9%) of patients without vitamin D deficiency had peptic ulcers, and the difference was statistically significant (P=0.011) (Table 1).

Peptic ulcers were detected in 38/291 (13%) of the patients who were included in the study. When the patients with and without peptic ulcers were compared, the mean age in both groups was 14 years. The mean vitamin D level was 15.8 ng/ml in patients with peptic ulcer, and 23 ng/ml in patients without peptic ulcer; and the difference was statistically significant (P=0.003). In total, 23/38 (61%) of patients with peptic ulcer had vitamin D deficiency, vitamin D deficiency was detected in 98/253 (39%) of patients without peptic ulcer, and the difference was statistically significant (P=0.723). HP positivity was detected in 27/38 (71%) of patients with peptic ulcer, and in 172/253 (68%) in the group without peptic ulcer, and no statistically significant differences were detected in this respect (P=0.723) (Table 2).

ROC Curve Analysis was performed to evaluate the diagnostic value of vitamin D levels for peptic ulcer. Classification success according to the AUC (Area Under the Curve) value (0.651±0.04) was found to be low. As a result of the Roc Curve Analysis, the best cut-off value was determined when vitamin D was less than and equal to 21 ng/ml for peptic ulcer. The sensitivity of this value was 68.42% (95% CI=51.3-82.5), and specificity was 58.50% (52.2-64.6). When the effects of other variables were eliminated with Regression Analysis, the significant effect of vitamin D continued (P=0.001).

Table 1. Comparison of demographic, hemogram, Helicobacter Pylori prevalence, and peptic ulcer presence in patients with and without Vitamin D deficiency.

Variables	Vitamin D Deficiency		P value
	Yes (n=121) Median [25%-75%]	No (n=170) Median [25%-75%]	
Age (Years)	15 [10 -16]	14 [10 -16]	0.352
White Blood Cell (Range: 4.5-1.5x10³/µL)	7820 [6680 -9420]	7720 [6080 -9080]	0.551
Hemoglobin (Range: 12-16 g/dl)	13.9 [13 -14.5]	13.95 [13.1 -14.7]	0.277
Platelets (Range:150-450x10³/µL)	319000 [256000 -366000]	294000 [262000 -343000]	0.118
	n (%)	n (%)	
Gender			0.040
Female	31 (25.6)	63 (37.1)	
Male	90 (74.4)	107(62.9)	
Helicobacter pylori	85 (70.2)	56 (32.9)	0.564
Peptic ulcer	23(%19)	15(%9)	0.11

Table 2. Comparison of Vitamin D level, Vitamin D deficiency, and Helicobacter Pylori prevalence in patients with and without peptic ulcer.

Variables	Presence of Peptic Ulcer (n=38)	Absence of Peptic Ulcer (n=253)	P
	Median [25%-75%]	Median [25%-75%]	
Vitamin D level (ng/ml)	15.8 [23 -11.4]	23 [27 -13.5]	0.003
	n (%)	n (%)	
Helicobacter Pylori	27 (%71)	172 (%68)	0.704
Vitamin D deficiency	23 (%61)	98 (%39)	0.011

Discussion

Vitamin D is a powerful immunomodulator playing roles in both natural and acquired immunity. Vitamin D increases antimicrobial peptide production. It was reported that people with low vitamin D levels have higher rates of tuberculosis infection with more severe progression [12]. It was reported in previous studies that people with vitamin D receptor polymorphism were more prone to tuberculosis infections [13]. It was reported in another study that people who received vitamin D had a lower HP prevalence than the group that did not receive vitamin D [14]. It was reported in another study conducted in Italy patients with autoimmune gastritis had lower vitamin D levels and higher HP levels [6]. In a study that was conducted by Surmeli et al. in Turkey, it was reported that vitamin D levels were lower in HP (+) group than in HP (-) group [15].

Hamid Nasri et al. reported in their study that vitamin D serum levels had positive effects on chronic inflammatory status in chronic hemodialysis patients, strengthening the immune response [16]. In another study, Kouichi Hosoda et al. reported that vitamin D could eradicate HP infection [17]. Yildirim et al. reported that patients with vitamin D deficiency had lower HP eradication rates [18]. A study that was conducted by Guo et al. in China showed that vitamin D receptors were involved in gastric mucosa homeostasis with effects protecting from HP infection [19]. In our study, it was found that HP prevalence was at similar rates in the group with and without vitamin D deficiency. Contrary to the results of previous studies, we did not find any association between HP and vitamin D deficiency.

It was reported in a previous study that vitamin D increases the tight connections between cells in cell cultures at significant levels, and maintains structural integrity. However, intestinal mucosal integrity is impaired in vitamin D receptor -/- mice. In the study in question, it was also reported that it can stimulate epithelium migration, playing critical roles in mucosal barrier homeostasis and maintaining the healing capacity of the colon epithelium [20]. Vitamin D stimulates cell differentiation, which is essential for cell growth and wound healing, reducing cell reproduction. Peptic ulcers are pathological lesions detected in

the upper gastrointestinal tract and mucosa, and can go as deep as to the submucosa. HP also plays roles in many factors, such as increased stomach acidity, non-steroidal anti-inflammatory drugs, stress, and 'O' blood type.

In the study by Zubair et al., it was reported that diabetic foot ulcers were more frequent in patients with diabetes and patients with low plasma vitamin D levels [21]. In a study conducted by Burkiewicz et al. to compare patients with and without leg ulcers, it was found that patients with leg ulcers had lower vitamin D levels [22]. A study that investigated relations between vitamin D levels and pressure ulcers found significant relations between vitamin D deficiency and pressure ulcers [23]. It was reported in the study by Joachim et al. that vitamin D support accelerates wound healing in patients with diabetic foot ulcers, and patients with diabetic foot ulcers are at risk for vitamin D deficiency [24]. In the present study, the average vitamin D levels were found to be lower, and the prevalence of vitamin D deficiency was higher in the group with vitamin D deficiency compared to the group without vitamin D deficiency. However, in the ROC analysis, the specificity and sensitivity of vitamin D deficiency were found to be low for peptic ulcer. The prevalence of vitamin D deficiency increases since nutritional problems and absorption disorders are also common in gastrointestinal tract diseases. For this reason, we believe that vitamin D deficiency may occur due to nutritional problems and absorption disorder in patients with peptic ulcers.

Many factors, such as geographical location, seasons, air pollution, exposure to the Sun, and dressing affect vitamin D synthesis through the skin [25]. Since the season in which a study is conducted will also affect the results, our study was designed to cover all seasons. The strong side of our study was that it is the first study examining the relations between the prevalence of peptic ulcer and HP, and vitamin D that affect the gastrointestinal tract in childhood. The limitation of our study was that conditions, such as diet and exposure to the Sun, which might affect vitamin D levels, were not known since it had a retrospective design.

Conclusion

No relations were detected between vitamin D levels and HP prevalence. Since vitamin D levels may be lower in patients who have peptic ulcer, vitamin D levels must be examined in such patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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